Mechanisms of aggression and production in chickens: genetic variations in the functions of serotonin, catecholamine, and corticosterone

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The neuroendocrine systems, such as dopamine (DA) and serotonin (5-HT) as well as corticosterone (CORT), are involved in regulating behavioural patterns and reproduction in humans and other mammals. Similar functions of neuroendocrine system may present in laying hens. To test the hypothesis, two divergent chicken lines were used in the study. Each line has distinct levels of aggressiveness and productivity at a group setting and exhibits differen susceptibility to various environmental stressors. We found that, at 21 wks of age, LGPS (Low Group Productivity and Survivability) birds had significantly higher blood concentrations of DA and epinephrine than the KGB birds (Kind Gentle Birds, also previously termed HGPS, birds with a High Group Productivity and Survivability) (P<0.01, respectively). The blood concentration of norepinephrine was not significantly different between the lines but the ratio of epinephrine to norepinephrine was higher in LGPS birds (P<0.01). The blood concentration of 5-HT was also significantly higher in LGPS birds compared to KGB birds (P<0.01). In contrast, KGB birds tended to have a higher level of blood CORT (P=0.1). The results suggest that genetic selection for productivity and survivability with domestic behaviours alters the birds' neuroendocrine homeostasis. The selection-associated plasticity of the neuroendocrine system in controlling animal aggression and productivity were discussed in the article.

Abbreviation Key: CNS = Central nervous system; CORT = Corticosterone; DA = Dopamine; DβH = Dopamine-β-hydroxylase; EP = epinephrine; DXL = Commercial Dekalb XL line; HA line = chicken line selected for high antibody response to SRBC; HAP axis = Hypothalamic-pituitary-adrenal axis; H:L = Heterophil:lymphocyte ratio; KGB = Kinder Gentler Bird selected for high group productivity and longevity; LA line = chicken line selected for high antibody response to SRBC; LH = luteinising hormone;

LHRH = luteinising hormone-releasing hormone; LGPS = chicken line selected for low group productivity and survivability; MHC = Major histocompatibility complex; NE = norepinephrine; RIA = radioimmunoassay; SRBC = Sheep red blood cell; TH = tyrosine

Introduction

Aggression, in nature, is associated with competition (natural selection) for survival and reproduction (Fraser and Rushen, 1987; Duncan, 1998). However, in artificial production environments, such as in poultry production, aggression causes increased social stress, feather and body damage, in some instances these injuries leading ultimately to cannibalism. Cannibalism is a major concern related non-beaktrimmed bird deaths in current housing environments (Appleby and Hogarth, 1991; Tablante *et al.*, 2000; Glatz, 2005; Rodenburg *et al.*, 2005). To prevent the expression of these injurious behaviours, it is necessary to understand the cellular mechanisms involved in regulating bird domestic behaviour and reproduction.

In humans and other mammals, alterations of neuroendocrine homeostasis have been thought to be a final common pathway in controlling individuals' behavioural patterns and productivity. Specifically, monoamine abnormities are found to be associated with aggressive behaviours (Berman and Coccaro, 1998) and alterative reproduction (Sharp *et al.*, 1984; Barraclough 1992). Serotonin (5-HT) and its metabolites, 5-hydroxyindoleacetic acid (5-HIAA) as well as density of its receptors have been used as major indicators of abnormal behaviours, including aggression (Valzelli, 1984; Bell and Hobson, 1994; Popova *et al.*, 1997; Barak and Mashiach, 2003; Abumariam *et al.*, 2006). In addition, 5-HT directly and indirectly affects reproductive performances (Tuomisto and Mannisto, 1985; Sirotkin and Schaeffer, 1997). Dopamine (DA) is another monoamine involved in controlling domestic behaviour and reproduction (Snider and Kuchel, 1983; Kudriavtseva *et al.*, 1988; Miczek *et al.*, 1994; Kuikka *et al.*, 1998), and dopaminergic receptor 2 (D_2) gene represents one of the few single-site loci associated with abnormal behaviours in human (Blum and Sheridan, 1995a, b). Catecholamines (like epinephrine, EP and norepinephrine, NE) and corticosterone (CORT), known as "stress hormones", are functionally involved in controlling domestic behaviours (Servo and Naumenko, 1990), linked to mood control (fight or flight), and engaged in cope-with-stress as a sense of well-being (Kopin, 1984; Rolih and Ober, 1995; Kilgour and Szantar-Coddington, 1997; Pollard, 1997). Biological dysregulation of these biogenic amines or hormones may cause brain structural as well as functional reorganization (de Kloet *et al.*, 1996; Ferris, 2000), which in turn affect animal's cope styles and well-being.

The present study was designed to determine if bird neuroendocrine system has similar functions in controlling aggression and production since there is evidence that suggests bird brains possess a core "social behavioural network" which is humongous to the social behavioural network of mammals (Goodson, 2005). In addition, there are similar distributions of neurotransmitter receptors, including dopaminergic and serotonergic receptors between birds and mammals (Dietl and Palacios, 1988; Richfield *et al.*, 1987; Walker *et al.*, 1991).

Two divergent chicken lines, KGB (kind gentle bird) and LGPS (low group productivity and survivability bird, previously termed MBB, mean bad bird), were used in the study. Each line has distinct leves of aggressiveness and productivity at a group setting and exhibits different susceptibility to environmental stressors (Hester *et al.*, 1996 a,b; Cheng *et al.*, 2001a,b; Cheng and Muir, 2005). The differences in behavioural and physiological characteristics of these lines may be reflected in changes in the capability of the neuronal system in response to stimuli. The objective of the study was to determine whether the

effects of selection on behavioural adaptation and productivity could lead to selection-associated functional alterations of the neuroendocrine systems in releasing endogenous psychotropic compounds, such as 5-HT, DA, and CORT; and to evaluate whether the changes of these monoamines and CORT an be used as physiological indicators of an animal's coping ability and well-being.

Material and methods

DEVELOPMENT OF THE GENETIC LINES

The process for developing the genetic lines, KGB and LGPS, has been described previously (Muir, 1996; Cheng and Muir, 2005). Briefly, a programme termed "group selection" was used for developing the research lines. The programme turns "survival of the fittest" emphasized on the individuals to "survival of the adequate" in the group. Results from group selection studies have showed that productivity can be increase while at the same time well-being improved.

The 8th generation was produced from mating 1248 hens with 312 roosters selected at random from 20 wk old pullets and roosters of the 7th generation. Eggs were collected for 2 weeks. Chicks were reared using standard management practices (Muir, 1996), and at 18 wks of age, 9216 pullets were housed by half-sib family in 768 12-birds cages. After 52 wks of production (72 wk of age), birds from 12 cages with the highest group productivity (egg number) and the lowest mortality form cannibalism and flightiness, along with their full and half sib brothers, were selected for the KGB line. To establish a comparison line, differing only in the criteria of selection, birds from 12 cages with the lowest group productivity and the highest mortality, along with their full and half sib brothers, were used to establish a reverse selected LGPS line.

Birds were randomly mated within each line, 4 hens/one rooster; avoiding full or half-sib mating to establish the 9th generation of the KGB and the 2nd generation of the LGPS lines which were used as the genetic material for this research. The detail of the selection technology and rearing programme was reported previously (Muir, 1996; Cheng and Muir, 2005). Pullets of each genetic line were not beak trimmed, and reared under the same conditions, *i.e.*, hatched, vaccinated for *Marek's* and *Newcastle's* disease, and maintained using standard management practices in raised wire cages up to 17 wk of age. At 17 wk of age, birds from each genetic line were randomly assigned to individual cages, each providing 1085 cm^2 per bird. Feed and water were provided for *ad libitum* consumption. Overhead lights were on daily from 0700 until 1900 h initially, and were increased by 15 min/wk. Light duration was at 13 h daily when the study was performed.

Chicken care guidelines were in strict accordance with the rules and regulations set by Federation of Animal Science Societies (Graig *et al.*, 1999). Experimental protocols were approved by the institutional Animal Care and Use Committee at Purdue University. Efforts were made to minimize animal suffering and the number of birds to be used.

BLOOD SAMPLING

Based on previous observations, the main behavioural adaptation of the KGB birds in responses to social stress became stable after the first 3 wks in responses to social stress (Craig and Muir, 1996a, b). At 21 wks of age, 24 birds from the KGB and LGPS lines, without a plumped egg confirmed by palpating, were bled between 09:00 and 10:00 h (Savory and Mann, 1997). A 5 ml blood sample was collected into a heparinised tube from the brachial vein of each bird within 2 min of removing from its cage. For measuring concentration of 5-HT, the whole blood was used. For measuring concentrations of catecholamines and CORT, blood samples were centrifuged at 700 *g* for 15 min at 20ºC

using Sorvall BC 3B plus centrifuge. Plasmas were kept on ice for further processing or kept at –80ºC until measurement.

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY ASSAY (HPLC ASSAY)

To measure blood concentrations of catecholamines, *i.e.*, DA, EP and NE, the ESA plasma catecholamine analysis kit was used. Briefly, duplicate plasma samples were acidified with 4M perchloric acid, followed by deproteinization with the supplied reagent. After centrifugation, the acid-supernatants with internal standard were added and absorbed onto an alumina minicolumn to bind the catecholamines. HPLC columns were then rinsed and eluted with the supplied solutions, respectively. Eluents were injected into the reverse-phase columns and catechols were detected by liquid chromatography with electrochemical detection. The mobile phase (75 mM Na_2HPO_4, 1.7 mM OSA, 25 µM EDTA, 10% CH_3CN and 100uL/L Triethylamine, adjusted to pH 3.00 with Phosphoric acid) flow rate was 1.3 mL/min. Catecholamine concentrations were calculated from a reference curve constructed using the provided standards. Concentrations were obtained as picograms per mL.

To measure blood concentration of 5-HT, whole blood samples were acidified in duplicate using 4M perchloric acid and freshly prepared 3% ascorbic acid. After centrifugation, the acid-supernatants were injected into the columns. The mobile phase flowed rate was 1.0 mL/min., and the concentration of 5-HT was calculated from a reference curve made using standard 5-HT.

RADIOIMMUNOASSAY

Total plasma CORT was measured in triplicate using a commercial ^{125}I-souble antibody CORT radioimmunoassay (RIA) kit with modification as company suggestion for using in birds and as previously described (Renden *et al.*, 1994; Kannan, 1997). In order to validate for parallelism and recovery in birds, adjustments of dilution to 1 to 5, were made, *i.e.*, 20 ul sample to 80 ul steroid diluent. The concentration of CORT was calculated from a reference curve that ranges from 0.1 ng/mL (83% binding) to 4.0 ng/mL (14.9% binding). Addition of known amounts of unlabeled CORT to plasma samples, *i.e.*, producing theoretical concentrations of 0.5, 1.0 and 2.0 ng/mL, resulted in 0.48, 1.08, and 1.97 ng/mL, respectively (CV = 5.0%). The sensitivity of the assay was 0.02 ng/mL. All samples within the experiment were performed at same time.

STATISTICAL ANALYSIS

The experimental design was completely randomized with genetic lines as the main effect. Results were assessed statistically using one-way ANOVA, and intergroup differences were analyzed by Newman-Keuls post hoc test.

Results

LINE DIFFERENCES IN PRODUCTIVITY AND SURVIVABILITY

Productivity and survivability were significantly different among the 8th generation KGB and LGPS lines as well as the overall line from which the selected lines came. The KGB birds had significantly higher productivity than the birds of the overall line which was in turn greater than the LGPS birds, in terms of egg number per cage housed, and egg mass per day per cage, but not egg weight (*P*<0.0 1, *Table 1*). In addition, mortality from cannibalism was significantly higher and survivability was greatly lower in the LGPS line compared to both KGB line and overall line (*P*<0.01, *Table 1*).

GENETIC SELECTION-INDUCED ALTERATIONS IN PLASMA CONCENTRATIONS OF SEROTONIN

Blood concentration of 5-HT were measured using HPLC (*Figure 1*), and the reference cures created using commercially purified 5-HT in this study was reliable and repeatable in duplicate running the samples ($R^2 = 1.0$, *Figure 1a*). There was a significantly higher blood concentration of 5-HT in the LGPS birds than in the KGB birds (1.43 *vs.* 1.18 mg/ml, *P<0.01*) (*Figure 1b*).

GENETIC SELECTION-INDUCED ALTERATIONS IN PLASMA CONCENTRATIONS OF CATECHOLAMINES

Genetic selection-induced different alterations of blood concentrations of catecholamines between the lines were shown in the *Figure 2* and *Table 2*. Based on the reference cure developed using commercial stand ($R^2 = 1.0$, *Figure 2a*), the LPGS birds exhibited higher concentrations of DA and EP as compared to the KGB birds, *i.e.*, 2.42 *vs.* 0.59 ng/mL (*P<0.01*) and 0.59 *vs.* 0.30 ng/mL (*P<0.01*), respectively (*Table 2*). The concentration of NE was not significantly different between the selected lines, but the ratio of EP/NE was significantly higher in the birds of the LGPS line (72.5% *vs.* 34.0%, *P<0.01, Table 2*).

GENETIC SELECTION-INDUCED ALTERATIONS IN PLASMA CONCENTRATIONS OF CORTICOSTERONE

Genetic heritability related changes of blood concentration of CORT were measured using IRA, and the selected line differences were presented in the *Table 2*. The mean blood concentrations of CORT were 1.84±0.19 and 1.49±0.21 ng/mL for the KGB and LGPS birds, respectively (*Table 2*). There was a trend showing a higher blood concentration of CORT in the KGB birds than in the LGPS birds.

Discussion

The results of the present study provide evidence that selection for group productivity and longevity with reducing cannibalism and flightiness in birds results in altering regulation of the neurochemical system, including changes in blood concentrations of 5-HT, DA, EP, NE, and CORT. The data is consistent with previous findings in mammalian research that domestication of animals is associated with hereditary reorganization of the neuroendocrine system (Naumenko *et al.*, 1987, 1989; de Kloet *et al.*, 1996; Ferris, 2000) and changes of neurochemical homeostasis (Bilzard *et al.*, 1983; Crusio, 1996). The present findings further support our hypothesis that positive changes in birds' domestic behaviours and productive performances resulting from selective breeding likely reflect changes in the link between the nervous and endocrine systems. That is, when selection pressure is applied to productivity and survival as well as associated domestic behaviours by reducing cannibalism and flightiness, the pressure is simultaneously applied to the neuroendocrine system, resulting in changes of physiologic functions that control coping ability such as improving survivability and productivity.

SEROTONIN AND SELECTION FOR HIGH PRODUCTIVITY AND LONGEVITY WITH REDUCING CANNIBALISM

There were different levels of serotonin concentrations between the lines selected for high or low productivity and survivability. The results are consistent with the hypotheses that serotonin has multifunctional roles in modulating many types of behavioural and physiological processes, including feeding, sexual and aggressive behaviour (Mench and

Shea-Moore, 1995; Weiger, 1997; Olivier *et al.*, 1998). Abnormalities of blood and brain 5-HT and its metabolite, 5-HIAA, as well as the density of its receptors have been used as major indicators of alterations in behavioural adaptability and reproduction (Bell and Hobson 1994; Dinan, 1996; Popova *et al.*, 1997; Maswood *et al.*, 1998; Abumaris *et al.*, 2006; Nomura and Nomaura, 2006).

Serotonin functions as an inhibitory factor of aggression in controlling domestic behaviour (Popova *et al.*, 1975). Depletion or decrease of 5-HT concentration and ratio of 5-HIAA/5-HT in the central nervous system (CNS) have been implicated in dysfunctional behaviours, including aggressiveness and violence in human and non-human animals (Higley *et al.*, 1996; Unis *et al.*, 1997; Parmigiani *et al.*, 1999; Popova *et al.*, 1999; Gollan *et al.*, 2005; Popova, 2006; Wrase *et al.*, 2006), and cannibalism in birds (Barofsky *et al.*, 1983). However, biological roles of blood 5-HT in behavioural adaptation and motivational regulation are unclear. Decreased, increased and unchanged blood 5-HT concentrations have been found in association with behavioural dysfunctions, including aggressiveness (Cook *et al.*, 1995; Hanna *et al.*, 1995; Moffitt *et al.*, 1998). The conflicting data from different investigations could be related to different genetic selection programmes, species, behavioural evaluations and stressors used as well as duration and frequency of stressor presentation. Our results that higher blood 5-HT level associated with lower survivability resulting from higher cannibalism and flightiness in the LGPS birds is consistent with our hypothesis that different patterns of secreting of blood 5-HT are associated with specific behavioural parameters. Blood 5-HT level, positively correlated with aggressiveness, were also found in adolescents with behavioural conduct disorder (Unis *et al.*, 1997), borderline mental retardation patients with impaired impulse control and stress-induced aggression (Lenders *et al.*, 1998), and dominant male monkeys (Steklis *et al.*, 1986; Raleigh *et al.*, 1991). The association between 5-HT levels and aggressive behaviours supports our view that blood concentration of 5-HT could serve as a physiological indicator of the animal's coping ability to stress as well as a biological trait marker for domestic behaviours. In support of this view, other studies have determined that blood 5-HT levels are under genetic regulation (Jerneij and Cicin-Sain, 1990: Cook and Leventhal, 1996), and its levels have been used as a stable marker in monitoring the course of certain dysfunctional behaviours (Stahl *et al.*, 1982), such as higher platelet 5-HT concentrations in schizophrenic patients (Muck-Seler *et al.*, 1999) and autism (Cook and Leventhal, 1996). Values of blood 5-HT also represent a heritable stable biological parameter in rodents (Jernej and Cicin-Sain 1990). As such rats, reverse selected for high and low platelet serotonin levels, were not affected by periodic oscillations, sex or age.

In the periphery, all 5-HT is stored in platelets (Anderson *et al.*, 1987; Jernej and Cicin-Sain, 1990), and platelet 5-HT is exchangeable with blood 5-HT but not brain 5-HT (Pietraszek *et al.*, 1992; Cook and Leventhal, 1996). Since the method used to measure 5-HT levels in platelets is to measure it in whole blood (Cook and Leventhal, 1996) and more than 99% of whole blood 5-HT is contained in platelets (Anderson *et al.*, 1987; Martin and Artigas, 1992), the two can be considered as belonging to a single compartment (Cook and Leventhal, 1996; Jernej *et al.*, 2000). Previous studies have shown that 5-HT systems between blood platelets and serotonergic neurons share some of anatomical and functional similarities (Stahl, 1977; Yan *et al.*, 1993), such as the active carrier mechanism, intracellular storage, receptors, and binding sites (Briley *et al.*, 1980; Paul *et al.*, 1980; Pletscher, 1988), platelets have been proposed as a peripheral tool for observation of central 5-HT system. However, the possibility of using platelets as a model system for brain neurons remains unclear. Previous studies have revealed that 5-HT levels in the CNS and peripheral tissues are genetically regulated differently (Popova, 1978; Lampagnani, 1986; Pietraszek *et al.*, 1992), and there are no correlations of either MAO activity (Young *et al.*, 1986; Virkkunen and Linnoila 1997) or 5-HT levels between brain

and platelet or blood (Popova, 1978; Takada *et al.*, 1996). Since 5-HT can not pass the brain-blood–barrier (Pietraszek *et al.*, 1992), blood and brain could be assumed as two compartments. About 90% of cerebral 5-HIAA effluxes directly into the blood (Pietraszek *et al.*, 1992) but there is no correlations between the changes in the **CSF** 5-HIAA and brain 5-HT (Martin and Artigas, 1992). These differences might be related to different mechanisms involve in regulating the uptake, synthesis and release of 5-HT between platelets and neurons (Chou *et al.*, 1983). For example, the binding potential (Bmax/Kd) of 5-HT 2A receptors on platelets was not correlated with that of brain, and changes of 5-HT2A receptors in platelets may not be a sign of similar changes in the CNS (Cho *et al.*, 1999). Ongoing studies in our laboratory aim to determine whether there are different cellular mechanisms underlying selection pressure-induced changes of 5-HT systems between periphery and brain in the presently selected lines.

The finding that LGP birds, compared to KGB birds, had higher concentrations of circulating 5-HT but lower productivity is consistent with the reports that 5-HT has a tonic, inhibitory effect on sexual behaviour and reproduction (Sirotkin and Schaeffer, 1997), such as inhibition of luteinising hormone (LH) secretion and ovulation (Nagatsuka, 1983; Morello *et al.*, 1992; Lorrain *et al.*, 1998). However, the roles of 5-HT in modulating sexual behaviour in female has been re-evaluated (Mendelson 1992), and is concluded that 5-HT can either inhibit or facilitate gonadotropins secretion, sexual hormone release, and sexual behaviour, which depends on which brain regions are involved (Nagatsuka, 1983; Gonzalez *et al.*, 1997; Wolf *et al.*, 1998), and what subtypes of 5-HT receptors are activated (Mendelson, 1992; Maswood *et al.*, 1998). As such effects of 5-HT on sexual behaviour were positively correlated to the stimulation of the pre-optic area (POA) and median eminence but negatively correlated to the stimulation of the ventromedial nucleus (VMN), zona incerta and arcuate nucleus (Gonzalez *et al.*, 1997). 5-HT2 receptors in the POA were involved in the stimulatory function of 5-HT, while 5-HT1A receptors mediated the inhibitory role in the VMN. Systemic injection of the selective 5-HT2 and 5-HT1 agonists, MK 212 and Ru 24969, sexual behaviour was facilitated and inhibited, respectively (Wilson and Hunter 1985). In addition, inhibited sexual behaviour was appeared by peripherally administrated 5-HT2 antagonist, pirenperone (Mendelson and Gorzalka, 1985), and its effect was attenuated by the 5-HT agonist, quipazine. At present, cellular mechanisms that hereditarily regulate productivity between the selected lines are unclear. A further study has been set up in our lab to investigate selection pressure-induced neuronal morphofunctional plasticity, including 5-HT system, associated with different reproductive capability of KGB and LGPS birds.

DOPAMINE AND SELECTION FOR HIGH PRODUCTIVITY AND LONGEVITY WITH REDUCING CANNIBALISM

At physiological condition, DA is released centrally as a neurotransmitter, and is processed peripherally as a precursor of NE (Kuchel, 1991). Since DA cannot cross the blood-brain barrier (BBB), circulating DA could be either from adrenal cells or from leukocytes (Bergquist *et al.*, 1998). However, during pathological condition, DA can be released from adrenomedullary chromaffin cells, and the adrenal glands can be transformed from an adrenergic to a dopaminergic source (Snider and Kuchel, 1983). Abnormalities in the blood and brain DA systems have been associated with dysfunctional behaviours as well as with declined coping ability with stress (Driscoll *et al.*, 1998; Kuikka *et al.*, 1998; van Erp and Miczek, 2006; Watt *et al.*, 2006). In agreement with such findings, the selected lines under a genetically selected pressure conducted with a social stressor resulted in bi-directional changes of both blood DA concentrations and coping abilities. KGB birds, selected for higher productivity and longevity with reducing cannibalism and flightiness, but not LGPS birds, had significantly lower blood level of

DA, and better and faster adaptation to various stressors (Hester *et al.*, 1996a, b). Our findings suggest that heritability variations for DA concentrations reflect individual coping strategies (Benus *et al.*, 1991a, b; Vogel and Harris, 1991; Driscoll *et al.*, 1998). Similar to our findings, DA concentrations (Dimsdale and Ziegler 1991; Hjemdahl, 1993; Rolih and Ober, 1995), and phenotype (Nikulina and Kapralova, 1991; Vadasz *et al.*, 1992; de Kloet *et al.*, 1996) have been used as indicators to evaluate the capability of animals in coping with stressors and well being. In the bi-directionally selected Roman high (RHA/Verh) and low (RLA/Verh) avoidance rats, increased DA activity occurred in the RHA/Verh rats, associated with increased locomotor activity, a marker of anxiety and stressful status (Driscoll *et al.*, 1990; Corda *et al.*, 1997). Similar results have been reported in rats exposed to uncontrollable electric tail-shock (Scott *et al.*, 1996). In addition, rats selected for swim-test resistance showed higher concentrations of DA compared to rats selected for swim-test susceptible, these higher levels of DA were correlated with higher struggling activity and larger decrease in home-cage ambulatory activity and water intake after shock. Based on the present and previous observations, the selection-induced differences in dopaminergic and behavioural responsiveness are consistent with an interpretation that coping strategies of selected breeds are based on the inheritance pattern and phenotypic correlations of behavioural, physiological and neuroendocrine variables (Castanon *et al.*, 1995).

DA has also been thought to be involved in controlling domestic behaviours (Kuikka *et al.*, 1998; Korzan *et al.*, 2006). In CNS, increased DA concentration was found in selected brain regions in both humans and rodents following aggressive or defensive activities (Lewis *et al.*, 1994; Miczek *et al.*, 1994; Kuikka *et al.*, 1998; Mersmann, 1998; Volavka *et al.*, 2004; van Erp and Miczek, 2006). Higher levels of DA were also found in the brain of Japanese quails with aggressive behaviour (Edens, 1987). In the periphery, dysfunctions of DA were also involved in aggressive behaviours of patients with mental deficiency (Marazziti *et al.*, 1996). Similarly, higher baseline blood DA levels in our selected LGPS birds could be associated with the reorganization of behaviours, *i.e.*, higher cannibalism and flightiness, resulting in higher mortality. In contrast, the lower baseline of blood DA in our KGB birds associated with sedate and passive behaviours, as well as lower cannibalism and flightiness. Our findings suggest that genetic selection pressures directly and indirectly influences regulation of the brain dopaminergic system, and turn the activation of the DA system into a favour to survival behaviour in KGB birds. Genotypic dependence of animals in controlling domestic behaviour has also been demonstrated in other species. Sgoifo and co-investigators (1996) reported aggressive rats with higher activity of catecholamine system and short attack latency. Similarly, other studies investigated changes in the pharmacological profile of DA system with dysfunctional behaviours. Footshock induced aggression in mice can be facilitated by DA administered centrally, and L-dopa, a DA precursor, administered peripherally (Datla *et al.*, 1992). Benus and co-investigators (1991a) also reported that aggressive male mice were more sensitive to apomorphine, a D2 receptor agonist, than non-aggressive male. Biting behaviour (Shaikh *et al.*, 1991), footshock induced aggression (Datla *et al.*, 1992), and fighting (Ossowska *et al.*, 1996) can be significantly facilitated by apomorphine, but were suppressed by spiperone (Shaikh *et al.*, 1991; Datla *et al.*, 1992) and raclopride (Dennis *et al.*, 2006), D2 receptor antagonists, and by the dopamine blockers, haloperidol and pimozide (Nikulina and Kapralova, 1992; Pant and Nath, 1993; De Leon, 1994). Data from these studies suggest that DA plays a significant role in controlling aggressive behaviour.

Birds of LGPS line had a lower productivity but higher blood concentrations of DA compared to counterparts of KGB line. These results are consistent with the hypothesis that dopaminergic system is one of the main inhibitory neuronal systems that control the

development of the reproductive systems (Becu-Villalobos and Libertun, 1995) and productivity (Sotowska-Brochocka *et al.*, 1994). Although identification of mechanisms that underlie the inhibitory effects of DA on productivity in present lines is unclear, previous experimental findings suggest that the regulation might be related to genetic selection pressure induced changes in physiological functions of the neuroendocrine system, including the HAP and hypothalamic-pituitary-gonadal (HAG) axes. Provided studies had shown that endogenous DA secreted in the hypothalamus exhibited catecholamine's tonic inhibition of Luteinising hormone-releasing hormone (LHRH) release (Contijoch *et al.*, 1992) and suppression LH secretion (Martin *et al.*, 1981). In rodents, the biological functions of DA on productivity had been confirmed by administrating exogenous DA that significantly reduced the LHRH level from the hypothalamus and lowered LH secretion from the pituitary (Tasaka *et al.*, 1985). Similar results were obtained from poultry studies. In hens, increase in dopaminergic activity inhibited the release of LH by exerting an inhibitory influence on the LHRH containing cells in the hypothalamus (Macnamee and Sharp 1989). The effects of DA could be related to increase in tyrosine hydroxylase activity (Thiery *et al.*, 1995) and activity of DA receptors (Andersson *et al.*, 1988). The later had been verified by either administrating of DA receptor agonist 2-Br-alpha-ergocryptine to lower plasma LH levels (Owens *et al.*, 1980) or blocking DA inhibitory effect by use of DA receptor blocker halperidol (Tasaka *et al.*, 1985).

Although it is unclear what mechanisms underlie the regulation of release DA peripherally in the presently selected birds, previous studies have reported that such release could be induced by stress-related unbalance of activities of enzymes involved in catecholamine metabolism (Kuchel, 1991). Stressor stimulates TH activity and, at the same time, inhibits activities of the enzyme dopamine-β-hydroxylase (DβH) that converts DA to NE (Kuchel *et al.*, 1982). If DβH activation cannot keep pace with activation of TH, DA synthesis predominates, and extra DA is released peripherally. Without detecting TH activities in the presently selected lines, we can not assume that LGPS birds have a higher TH activation. However, previous studied have shown that TH activation can be increased by selection for domestic behaviour in animals (Dygalo *et al.*, 1988; Kulikov *et al.*, 1989), and that hereditary based stress triggers different regulations of gene expressions for catecholamine biosynthetic enzymes in the adrenal medulla (Nankova and Sabban, 1999).

EPRINEPHRINE AND NOEPRINEPHRINE AND SELECTION FOR HIGH PRODUCTIVITY AND LONGEVITY WITH RADUCING CANNIBALISM

EP is released almost exclusively from the adrenal medullar, with a small amount synthesized in the brain, while NP is released from sympathetic neurons, with significant amount synthesized in the CNS, especially, in the hypothalamus (Bullock *et al.*, 1995). As "stress hormones", both EP and NE participate in a number of physiologic and pathologic processes, including regulation of emotion and motivation in response to stimulations. Changes in EP and NE levels, as well as the ratio of EP/NE have been used as indicators of the 'organisms' well-being and capability of cope to stress (Goldstein, 1981). In response to stimulations from selected pressure, the lower blood concentration of EP and lower ratio of circulating EP/NE found in KGB birds is consistent with the multifunctional roles of EP and NE. In contrast, the LGP birds had a higher blood concentration of EP and higher ratio of EP/NE, which correlates with their lower productivity and higher mortality from cannibalism. Furthermore, the ratio of EP/NE has been used as an indicator of well-being. A higher EP/NE ratio had been found in severely ill patients (Lechin *et al.*, 1996), stressful states (Vollmer, 1996; Piercecchi-Marti *et al.*, 1999), and dominant male monkeys (Dillon *et al.*, 1992). Collectively, these data support our hypothesis that genotypic or phenotypic variation of the EP/NE, in response to selection, may reflect

individual coping strategies that control changes in the animal's behavioural patterns.

In the present study the major factor causing the EP/EN increase in LGP birds was higher concentration of EP, since there was not significantly different in the concentrations of NE between the lines. A similar upregulation of EP concentration by increased biosynthesis was found in turkeys selected for higher adrenal response to cold stress (HL) (Brown and Nestor, 1974). Birds of the HL line also, similar to the LGP birds, laid significantly less eggs and had hyperactivity and poorer feeding efficiency. The present and previous results support the notion that genetic selection for various physiological indexes could have altered the effects of the central and peripheral dopaminergic system in an attempt to adapt to stress. It could mean that EP/NE can be used as an indicator for selecting trail and evaluate the animal's well-being.

CORTICOSTERONE AND SELECTION FOR HIGH PRODUCTIVITY AND LONGEVITY WITH REDUCING CANNIBALISM

Corticosterone is released from the adrenal cortex, the rate of its secretion being controlled by activation of the hypothalamic-pituitary-adrenal (HPA) axis via a double negative feedback loop. During pathologic conditions, such as under various stressors including social stress, concentration of CORT can be increased by overriding the HAP control system. As one of the "stress hormones", CORT has multifunctional roles in both normal and abnormal states, including regulation of the organism's behavioural patterns, coping styles and well-being.

Although differences in the baseline concentration of CORT were not found here to be significant, there was a tendency for CORT concentration to be higher in KGB birds than in those of the reverse selected line. The heritably different levels of CORT between the present selected lines could be the results of genetically different regulations in CORT secretion as induced by selected pressure. Supporting our findings, the value of circulating CORT has been used as a genetic selection criterion for evaluation of coping ability in responsiveness to stress, such as in open-field exposure (Jones *et al.*, 1992), physical and manual restraint (Mills and Faure, 1991, Jones and Satterlee, 1996; Savory and Mann, 1997), fear of humans (Jones *et al.*, 1994), cold and heart temperature stimulation (Brown and Nestor, 1974; Hester *et al.*, 1996a), and resistance to infection and inflammation (Gross and Colmano, 1971). Based on these observations, changes of CORT levels associated with different behaviours are a hereditary hallmark of the organism's responsiveness to stressors, and effects of CORT on stress-induced organism's responsiveness may depend on its levels, *i.e.*, a level slightly or excessively changed from its physiological basis, which could protect or destruct the organism's coping capability (Sapolsky and Meaney, 1986; Jones and Satterlee, 1996). The higher CORT concentration in KGB birds than in LGPS birds (1.84 *vs.* 1.49 ng/ml, P=0.1) might be at the high end of physiologic levels. Higher baseline levels of CORT signal a slight hyperactivity of the CORT system in KGB birds compared that in LGP birds, which is consistent with the previous findings that KGB birds had greater adrenal weights compared to those of control line (Hester *et al.*, 1996c). This view is further supported by observations in domestic Larger White pigs (Fernandez *et al.*, 1994; Blanchard *et al.*, 1993) and aggressive rodents (Korte *et al.*, 1996). As such a tendency to higher baseline plasma cortisol levels was found in subordinated pigs and in mice with longer attack latencies as compared with those aggressive counterparts, respectively. In addition, Shively and Kaplan (1984) determined that the subordinate Macaca fascicularis had heavier adrenal glands with higher plasma glucose levels but less atherosclerosis than those of dominants. The above findings suggest that upregulation of the adrenal system in KGB birds is part of a defence mechanism against environmental challenges, which may underlie their higher survivability, sedate and passive behaviours, and better coping to social, handling and

environmental stressors (Hester *et al.*, 1996a, b; Muir and Craig, 1996). Without stress challenges, we can not assume that KGB birds have a lower reactivation of CORT system in responses to stimuli. However, Sapolsk (1990) reported that, compared to high ranking adult male baboons, low ranking males had a higher basal cortisol and lower cortisol in response to the challenges of capture and corticol-releasing factor (CRF). Collectively, these results are consistent with the notion that adrenal hypertrophy may be an indicator of greater adaptation to stress (Siegel, 1971). Therefore, alterations in regulation of adrenocortical activity appear to be essential in controlling of coping activity and styles, as well as mobilization of body energy sources such as glycogen and triglyceride in response to stressors (Gaillard and Al-Damluji, 1987; Tempel and Leibowitz, 1994).

CORT defensive response to stress in KGB birds could be associated also with its role as an immunomodulator. As such following challenges with Escherichia coli, infection can be prevented by pre-treatment with CORT (Gross and Colmano, 1970). CORT can also protect the organism from damage by an excessive response of its immune system (Gross and Colmano, 1970; Munck *et al.*, 1984). Our data and others are consistent with the notion that, under physiologic condition, one of the primary roles of endogenous glucocorticoids may be immunomodulation rather than immunosupression (Dhabhar *et al.*, 1994); and that small increases in levels of glucocorticoid may enhance immune functions (Stanulis *et al.*, 1997). Thus in one of our parallel studies has found that KGB birds had an inherited basis of higher cellular-modulated immunity than that of LGPS birds (Chen *et al.*, 2000), In contrast, LGPS birds had higher levels of circulating immunoglobulin G and higher ratios of circulating Heterophil/lymphocyte. The different inherited characteristics of immunity could be associated with better and faster adaptability to various stressors as reported previously (Hester *et al.*, 1996a, b). In addition, except for the direct effects of CORT on animal behaviours such as aggression (Bonson *et al.*, 1994; Kruk *et al.*, 1998), the sedate and passive behaviours of the KGB birds could also related to indirectly effects through the regulating serotonergic system (Chaouloff, 1995; Joels *et al.*, 1995). Thus, the effects of CORT may enhance brain serotonergic turnover (Summers *et al.*, 2000), increasing 5-HT formation from tryptophan (Millard *et al.*, 1972), and affect the activity of 5-HT receptors (Mendelson and McEwen, 1992). Collectively, these results are consistent with the protective functions of CORT and could be, at least partly, related to natural mechanisms permitting animals to remain alert and keep physiological homeostasis in response to relevant stimulators.

Conversely, CORT could have inhibitory effects on the animal's coping ability, and negative influence physical parameters have been reported. For example, there were approximately 2-3 folds significantly higher concentrations of CORT in birds genetically selected for high adrenal response (HL) in response to mechanical restraint, compared to that in birds of the low response line (Brown and Nestor, 1974). Birds of the HL failed to maintain physiologic homeostasis, including slower growth (Brown *et al.*, 1959), overstated fear (Jones *et al.*, 1992; Jones and Satterlee, 1996), were higher excitable (Brown and Nestor, 1973, 1974), laid fewer eggs, and had higher natural mortality (Brown and Nestor, 1974).

A higher productivity and a tendency for CORT concentration to be higher in KGB birds compared to those of LGBS line suggest that CORT may have functions in regulating productivity of hens. The hypothesis is consistent with previous findings that the ovary is the one of the most probable target tissue for CORT (Etches *et al.*, 1983). CORT may exert its ovulation-inducing effect directly on the mature follicle (Etches *et al.*, 1984; Lang *et al.*, 1984) through an anatomical juxtaposition of the left ovary and adrenal gland (Etches *et al.*, 1984), or may alter the responsiveness of ovarian tissue to gonadotropins through modulating the reaction of the hypothalamus to tropic stimuli (Etches *et al.*, 1984). A previous study has demonstrated that CORT involves in the preovulatory surge of LH

which results in the first egg of a sequence (Sharp and Beuving, 1978). On the other hand, effects of CORT on productivity may through affects the serotonergic, dopaminergic systems or both which have been known to be involved in regulation of reproduction (Summers *et al.*, 2000; also see above discussion). In addition, CORT has impact on inflammatory and immunological processes (Gaillard and Al-Damluji, 1987). At physiological levels CORT enhance immune functions (Stanulis *et al.*, 1997), and protects organisms from reaching excessive immune reactive levels to cause damage to itself (Munck *et al.*, 1984), or inhibit autoimmunity which has be identified as one of the major reasons of impaired productivity (Bacon, 1987). Furthermore, previous studies have evidenced that CORT has important effects on caloric intake. Under normal condition, endogenous CORT involves in controlling ingestion and metabolism (Tempel and Leibowitz, 1994), such as catabolic effects on carbohydrate, fat and protein to maintain glucose homeostasis. Whether higher blood concentration of CORT in KGB birds affect feed efficiency is unclear, previous study had shown that KGB birds fed more, at least at first three weeks during the initial adaptation to layer house cages, than those of commercial lines (Craig and Muir, 1996b). The better feeding behaviours of KGB birds may be associated with their better adaptability to a variety of stressors (Hester *et al.*, 1996a, b), and their higher productivity. Currently, it is unclear whether LPGS birds have more active adrenal system in synthesizing CORT in response to stress, but previous study in the Syracuse high- (SHA) and low-avoidance (SLA) strains of rats has shown that, in response to stress, the SHA rats with smaller adrenals had larger responses of the HPA axis (Brush *et al.*, 1991).

Taken together, these data suggest that the effect of CORT on the animal's coping ability is biphasic and dependent on its concentration, which results in its attempt to engage or avoid environmental challenges, *i.e.*, at physiological levels it can protect the organism to cope with stressors, whereas at pathological levels it results in declining coping ability. Stress-induced reactions of the CORT system may be dependent on the species, breeds and stressors used as well as duration and frequency of stressor presentation. Although conflicting results have been reported, there is consensus as to the cellular mechanisms which regulate CORT secretion, *i.e.*, mediators are from the HPA axis. Alterations in the levels of corticotrophin-releasing hormone (CRH) and adrenocorticotropin (ACTH) control CORT secretion from adrenal glands (Rots *et al.*, 1995). Our present data support the view that individual differences in coping styles is coherent with a set of functions of the neuroendocrine system that underlies behavioural characteristics (Sgoifo *et al.*, 1996).

In conclusion, the present study demonstrates that selection for high and low group productivity and longevity with alterations in cannibalism and flightiness affected the regulations of the neuroendocrine system of selected birds, and that CORT and monoamines, such as 5-HT, DA, EP and NE, were differently regulated by selection pressure. Compared to the reverse selected birds, KGB birds selected for higher productivity and longevity with higher domestic behaviours, *i.e.*, low cannibalism and flightiness, may have a positive alterations in the neuroendocrine system, *i.e.*, lower blood concentrations of 5-HT, DA and EP, and higher levels of plasma CORT, which may be associated with their better coping to a novel environment and greater resistance to stressors. The unique homeostatic characteristics of each selected line may provide a neurobiological basis for investigating effects of genetic factors on physiological functions of biogenic amines involved in productivity and longevity related to domestic behaviours. The present data and data from others suggest that blood 5-HT, DA and EP as well as ratio of EP/NE, can be used as physiological indicators for genetically selecting birds with great resistance to social stress to eliminating beak trimming. This finding could be extended to other farm animals for improving their well-being.

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Table 1 Effect of genetic selection on survivability and productivity in hens.

Group	Survivability		Productivity		
	Longevity (Days)	Mortality (%)	Egg Number (Per Cage)	Egg Mass (Per Cage, g/day)	Egg Weight (g/each)
KGB	363[a] ± 0.4	1.3[a] ± 0.1	3543[a] ± 139	574[a] ± 24	59.4[a] ± 0.6
LGPS	193[b] ± 21.	8.6[b] ± 0.5	1297[b] ± 140	208[b] ± 22	58.9[a] ± 0.8
Overall	329[c] ± 2.0	2.3[c] ± 0.1	2850[c] ± 26.9	450[c] ± 4.4	57.8[a] ± 0.1

1) [a,b,c]Lines with different superscript are significantly different (*P*<0.01).
2) Values represent the Mean ± SEM. The line "Overall" was based on the mean of 768 colony cages (9216 birds), and the KGB and LGP line were based on the mean of 12 cages (144 birds) of each line, respectively.

Table 2 Genetic selection-induced alterations in blood concentrations of serotonin catecholamines, and corticosterone in hens.

Groups	DA (ng/ml)	EP (ng/ml)	NE (ng/ml)	EP/NE (Ratio, %)	CORT (mg/ml)
KGB	0.59 ± 0.08[a]	0.30 ± 0.06[a]	0.86 ± 0.12	34.0[a]	1.87 ± 0.19
LGPS	2.42 ± 0.76[b]	0.59 ± 0.13[b]	0.84 ± 0.13	72.5[b]	1.49 ± 0.21

[a,b]Means within a column with different superscript are statistically different (P<0.01).
The KGB and LGP lines were selected from high and low productivity and survivability resulting from cannibalism and flightiness. 5-HT, serotonin; DA, dopamine; EP, Epinephrine; and NE, Norepinephrine.
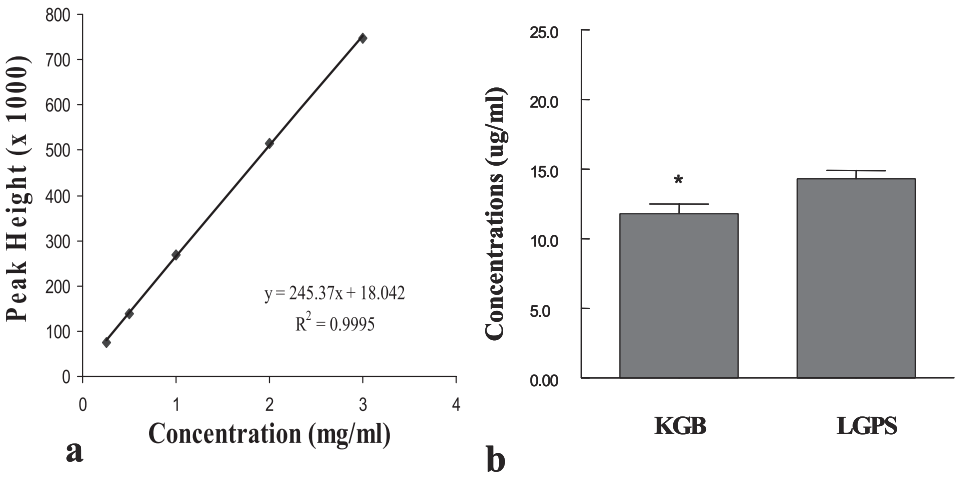
Figure 1 Quantity analysis of blood serotonin levels using HPLC. a) calibration curve, and b) effect of genetic selection on the blood concentration of serotonin. Asterisk indicates significantly different between selected lines. P<0.01.
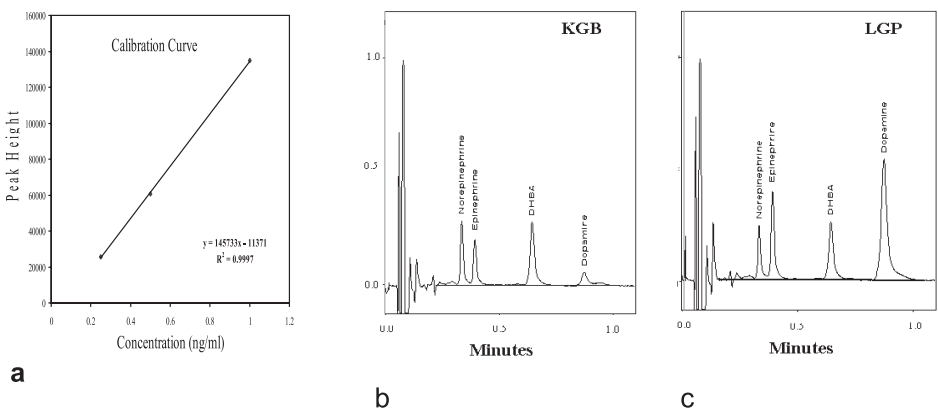

Figure 2 Examples of effects of genetic selection on blood concentrations of dopamine, epinephrine and norepinephrine. a) calibration curve, b) data from the KGB bird, and c) data from the LGP bird. The peak height of each neurochemistry in each graph was referred to its concentration based on the calibration cure, respectively.